UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,670	02/12/2007	Jeffrey D. Rothstein	46594-0004-01-US	5779

23973 7590 04/29/2011

DRINKER BIDDLE & REATH
ATTN: INTELLECTUAL PROPERTY GROUP
ONE LOGAN SQUARE, SUITE 2000
PHILADELPHIA, PA 19103-6996

EXAMINER	
FISHER, ABIGAIL L	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
04/29/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DBRIPDocket@dbr.com
penelope.mongelluzzo@dbr.com

Office Action Summary	Application No.	Applicant(s)	
	10/576,670	ROTHSTEIN ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-36* is/are pending in the application.

4a) Of the above claim(s) *33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-32 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/21/06; 2/2/07; 4/6/07; 8/4/08; 10/29/08; 5/20/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Response to Election/Restriction filed on February 22 2011 is acknowledged. Claim 8 is cancelled. Claims 1-7 and 9-36 are pending.

Election/Restrictions

Applicant's election of amyotrophic lateral sclerosis (ALS) and riluzole in the reply filed on February 22 2011 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-7 and 9-36 are pending in the application. Claims 33-35 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention (species), there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 22 2011. Accordingly, claims 1-7, 9-32 and 36 are being examined on the merits herein.

It is noted that applicants indicated that claim 35 read on the elected species. However, applicants elected ALS which is not a psychiatric disorder (depression or bipolar disorder). Therefore, claim 35 is withdrawn as being directed to a nonelected invention.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/21/06, 2/2/07, 4/6/07, 8/4/08, 10/29/08 and 5/20/09 was considered by the examiner.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR §§1.821(a)(1) and (a)(2). See, for example, sequence listing filed on 4/21/06. However, this application fails to comply with the requirements of 37 CFR §§ 1.821 through 1.825 because it lacks a statements under 37 CFR §§ 1.821(f) and (g), and

SEQ ID Nos cited along with each sequence in the specification or Figures. Applicants are also reminded that SEQ ID Nos are not required in Figures per se, however, the corresponding SEQ ID Nos then are required in the Brief Description of the Drawings section in the specification. Applicants are also reminded that a CD-ROM sequence listing submission may replace the paper and computer readable form sequence listing copies. Specifically, the sequence listing filed 4/21/06 lists 4 human DNA sequences but there is no supporting disclosure in the specification describing what they are. As such, it is unclear why these sequences are a part of the instant application. Applicants amended the specification on 1/18/07 removing the description of the sequence. It is recommended that applicants add back to the specification the description as originally filed (original specification, brief description of drawings, page 7, "SEQ ID Nos: 1-4 are EAAT2 promoter sequences"). Applicant(s) are given the same response time regarding this failure to comply as that set forth to respond to this office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

Claim Objections

Claim 16 is objected to because of the following informalities: the word "of" is missing between "consisting" and "Parkinson's" in line 2 of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-7, 9-10, 14-19, 21-32 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The specification, while being enabling for treating ALS with riluzole, ceftriazone and clavulanic acid, does not reasonably provide enablement for treating ALS with all beta-lactam containing compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, the specification does not teach that all compounds possessing a beta-lactam moiety would be expected to treat ALS.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Formal, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention and relative skill level

The invention relates to treating ALS with beta-lactam compounds. The relative skill of those in the art is high, that of an MD or PHD.

The state and predictability of the art

The art however is unpredictable. As illustrative of the state of the art, the examiner

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

cites Wermuth (Drug Discovery Today) and Tikka et al. (Journal of Neurochemistry, 2001, cited on PTO Form 1449).

The beta-lactam compounds can be interpreted as analogs (i.e. all compounds would possess the same core (beta-lactam) but different side groups). Wermuth teaches that small changes in chemical structure can lead to different chemical activity (see page 349, last paragraph right column; Figure 2, page 350; and Table 1, page 353, for example). Tikka et al. postulate that the activity of ceftriazone (a beta-lactam compound) in terms of protective functions (i.e. treatment of neurodegenerative disorders such as ALS) unrelated to its antimicrobial action is due to the side of D-α-aminoadipic acid not necessarily the beta-lactam portion (page 1413, left column, first complete paragraph).

The breadth of the claims

The claim is very broad insofar as it recites treating ALS with any compound that possess a beta-lactam. It is noted that beta-lactams are not limited to only be beta-lactam antibiotics. Ravikumar et al. (US Patent No. 6084082) teach beta-lactam nucleic acids as diagnostic agents. Davis et al. (USPGPUB No. 20030053981) teach beta-lactams as sterol absorption inhibitors (paragraph 0011). The claim is broad insofar as it recites treating ALSO with any beta-lactam compound with no indication of a structure-function relationship (i.e. moieties required to produce activity).

The amount of direction or guidance provided and the presence or absence of working examples and the quantity of experimentation necessary

The specification provides no direction or guidance for treating ALS with all beta-

lactam compounds. No reasonably specific guidance is provided concerning useful therapeutic protocols for treating ALS with all beta-lactam compounds, other than claiming such. Treatment of ALS with certain beta-lactams (ceftriazone and clavulanic acid) is corroborated by the working examples or the art. Since small changes in chemical structure can lead to different chemical activity as taught by Wermuth, one of ordinary skill in the art would have to undergo undue experimentation in order to determine which beta-lactam containing compounds would be expected to treat ALS. One of ordinary skill in the art would have to undergo undue experimentation as the specification does not teach a structure-function relationship between the beta-lactam compounds and their ability to treat ALS and therefore one of ordinary skill in the art would have to test each and every possible beta-lactam compound to determine its efficacy in treating ALS.

Conclusions

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed beta-lactam compound genus could be predictably used to treat ALS as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1-7, 9-32 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The specification, while being enabling for treating ALS with the antibiotic ceftriazone, does not reasonably provide enablement for treating ALS by administering ceftriazone in an amount which does not result in substantial clinically effective antibiotic activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Specifically, the specification does not teach the claimed amounts of the beta-lactam compound, ceftriazone, administered does not result in substantial clinically effective antibiotic activity or what dosage ranges do not give substantial clinically effective antibiotic activity.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[2]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Formal, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention and relative skill level

The invention relates to treating ALS with beta-lactam compounds. Specific beta-lactam compound claimed is ceftriazone. The claimed amounts are less than about 500 mg/day. Also claimed is administering to the subject a therapeutic amount of a beta-lactam compound to treat ALS but an amount which does not result in

[2] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

substantial clinically effective antibiotic activity. The relative skill of those in the art is high, that of an MD or PHD.

The state and predictability of the art

The specification exemplifies treating ALS with ceftriazone. The ceftriaxone is administered in an amount of 10 mg/kg intravenous once per day (page 33 of specification). The specification also teaches that the term clinically effective antibiotic amount refers to the amount of ceftriaxone that has clinically useful activity in the treatment or prevention of bacterial growth in a subject (page 21-22). The specification teaches that ceftriazone is typically administered for antibiotic therapies in doses of 0.5 to 4 grams intravenously or intramuscularly once per day (page 20). Additionally, Hansfield et al. (Sexually Transmitted Diseases, 1994) teaches that 250 mg intramuscularly of ceftriaxone is effective in treating uncomplicated gonorrhea (Abstract). Therefore, doses of 250 mg would be expected to produce clinically effective antibiotic activity. Hoosen et al. (South African Medical Journal, 2002) teach single low-dose ceftriaxone for the treatment of gonococcal ophthalmia. It is taught that low doses namely 62.5 mg for babies and 125 mg for mothers is effective for the treatment of gonococcal ophthalmia (abstract). Therefore, doses of 62.5 mg and 125 mg would be expected to produce clinically effective antibiotic activity.

The breadth of the claims

The claim is broad insofar as it recites treating ALS with beta-lactam compounds (which are known in the art to be antibiotics) in an effective amount but an amount which does not result in substantial clinical effective antibiotic activity. However, the

dosage claims 500 mg/day would be expected to produce clinically effective antibiotic activity based on the teachings of the specification (500 mg is lower amount taught there) and the art (wherein 250, 125 and 62.5 mg produced clinically effective antibiotic activity).

The amount of direction or guidance provided and the presence or absence of working examples and the quantity of experimentation necessary

The specification provides no direction or guidance for treating ALS with an amount of ceftriaxone which is not an amount that would be expected to produce clinically effective antibiotic activity. The working example utilizes ceftriaxone in amount greater than instantly claimed and in an amount that would be expected to produce clinically effective antibiotic activity based on the teachings of the instant specification and Hansfield et al. One of ordinary skill in the art would have to undergo undue experimentation because they would first have to determine an amount of ceftriaxone that does not produce clinically effective antibiotic activity and then determine if that amount could be useful in treating ALS as the amounts known to treat ALS would also be expected to produce clinically effective antibiotic activity.

Conclusions

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat ALS in an amount which does not produce clinically effective antibiotic activity as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the

patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claims 1-7, 9-32 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantial" in claim 1 and 18 is a relative term which renders the claim indefinite. The term "substantial" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "substantial clinically effective" indicates a certain range is acceptable. However, the specification does not discuss nor contemplate what is the minimum or maximum range for "substantial clinically effective".

Claim 6 as currently written is vague and indefinite. The claim recites "at least about" 6 months. At least provides a static point and about provides a dynamic point and cannot be used to modify one another. It is not clear from the claims or the specification what "at least about 6" means since 5 months would be "about 6 months", but would not be "at least" 6 months. This renders the claim indefinite because the term "at least about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be

reasonably apprised of the scope of the invention. Given the above reasons, the metes and bounds of the claims cannot be determined.

Claims 7 and 28-30 as currently written is vague and indefinite. The claims recite "less than about" 500 mg/day, "less than about " 250 mg/day, "less than about" 100 mg/day and "less than about" 50 mg/day. Less than provides a static point and about provides a dynamic point and cannot be used to modify one another. For example, it is not clear from the claims or the specification what "less than about 500" means since 501 months would be "about 500", but would not be "less than" 500. This renders the claim indefinite because the term "less than about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Given the above reasons, the metes and bounds of the claims cannot be determined. Claim 9 is indefinite for similar reasons as it recites "does not exceed about 10".

Claims 2-5, 10-17, 19-27, 31-32 and 36 are included in the rejection as they depend on a rejected base claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 9, 16-18, 28-30 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel (USPGPUB No. 20040014739, cited on PTO Form 1449).

Applicant Claims

The instant application claims a method of treating a subject suffering from or susceptible to ALS (elected species), the method comprising administering to the subject a therapeutic amount of a beta-lactam compound which is sufficient to treat the disease or disorder.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Koppel claims a method of treating a human patient afflicted with a condition characterized at least in part by abnormal extracellular glutamate concentration in the brain or other nervous tissue. The method comprises administering to a patient a composition comprising a neurologically effective amount of a clavulanic acid compound (claim 7). The condition as claimed includes amyotrophic lateral sclerosis (ALS) (claim 8). The structure of clavulanic acid is shown in paragraph 0135. It is a beta-lactam compound. Parenteral administration is claimed (claim 15). Parenteral routes of administration include intramuscular and intravenous administration (paragraph 0130). Typically the dosage levels for beta-lactams is less than necessary to achieve clinically effective antibacterial levels. Parenteral dosages can range from about 1 to about 80 mg per dose (paragraph 0123). It is taught that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state (paragraph 0133). The plasma concentration is around 50 pM (paragraph 0146).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Koppel teaches that the beta-lactam compound clavulanic acid can be utilized to treat ALS, Koppel do not exemplify treating ALS with clavulanic acid.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize clavulanic acid to treat ALS. One of ordinary skill in the art would have been motivated to utilize clavulanic acid to treat ALS as Koppel suggest utilizing clavulanic acid to treat neurological disorders such as ALS. Therefore, based on the teachings of Koppel when desiring a treatment method for ALS, it would have been obvious to one of ordinary skill in the art to parenterally administer clavulanic acid.

Regarding the claimed amount of beta-lactam compound, Koppel teach overlapping amounts. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. **See MPEP 2144.05 [R-5].**

Regarding the claimed length of administration, Koppel teaches that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state. Therefore, the length of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable

ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art to utilize a kit for the administration of the clavulanic acid. One of ordinary skill in the art would have been motivated to utilize a kit in order to package and ship the formulation as well as to provide instructions for a consumer/provider on how to utilize the product. "Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." *In re Ngai*, 367 F.3d 1336, 70 USPQ2d 1862 (Fed. Cir. 2004). **See MPEP 2112.01 [R-3].** The applicant has not indicated that the instructions indicate some unobvious functional relationship between the product and the instructions.

Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel in view of Miller et al. (Neurology, 1996, cited on PTO Form 1449).

Applicant Claims

The instant application claims administering riluzole in combination with the beta-lactam compound.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Koppel are set forth above. Specifically, Koppel teach administering clavulanic acid to treat ALS.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Koppel does not teach administering clavulanic acid in combination with riluzole. However, this deficiency is cured by Miller et al.

Miller et al. teach that riluzole is the firs drug approved by the FDA for use in treating ALS (abstract).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel and Miller et al. and utilize riluzole in combination with clavulanic acid. One of ordinary skill in the art would have been motivated to utilize this combination as both are taught as drugs useful for the treatment of ALS. As a general principle it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose, the idea of combining them flows logically from their having been individually taught in the prior art. See *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) **MPEP 2144.06.**

Claims 14-15 and 21-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel in view of Bristol et al. (Annals of Neurology, 1996, cited on PTO Form 1449).

Applicant Claims

The instant application claims EAAT2 protein expression is increased. The instant application claims determining of level of EAAT expression in the subject.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Koppel are set forth above. Specifically, Koppel teach administering clavulanic acid to treat ALS. The disease is a condition characterized at least in part by abnormal extracellular glutamate concentration in the brain or other nervous tissue. It is taught that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Koppel teach treating diseases associated with abnormal extracellular glutamate concentration, Koppel does not teach measuring EAAT expression or increasing EAAT2 expression. However, these deficiencies are cured by Bristol et al.

Bristol et al. is directed to glutamate transporter gene expression in amyotrophic lateral sclerosis motor cortex. Defects in functional glutamate transport have been identified in ALS brain and spinal cord. Tissue culture studies mimicking the loss of glutamate transporter suggests that defective glutamate transport in ALS could account for, or at least contribute to, motor neuron degeneration (page 676, left column). Three

glutamate transporter subtypes where cloned including the human equivalents EAAT1, EAAT2 and EAAT3. The changes in glutamate transport in ALS were found to be specific for the GLT-1 subtype (EAAT2) as revealed by a large loss of the transporter protein (right column, first paragraph). It is postulated that the loss of GLT-1 protein (EAAT2) could account for elevated CSF levels of glutamate and could propagate motor neuron degeneration in ALS (page 678, last paragraph).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel and Bristol et al. and measure EAAT expression before and after administration of the beta-lactam compound. One of ordinary skill in the art would have been motivated to measure EAAT expression before administration to aid in diagnosing ALS as Bristol teaches that low levels of EAAT protein expression are shown in ALS patients. One of ordinary skill in the art would have been motivated to measure the levels of EAAT expression to determine if correction to glutamate transport is seen. Since both Koppel and Bristol et al. recognize that ALS is associated with defective glutamate transport, it would have been obvious to one of ordinary skill in the art to monitor EAAT protein expression during the course of therapy.

Regarding the claimed level of EAAT2 production, although Koppel does not disclose all the characteristics and properties of the composition disclosed in the present claims, based on the substantially identical process using identical components

(same drug (beta-lactam) in the same or overlapping amount), the Examiner has a reasonable basis to believe that the properties claimed in the present invention are necessarily present in the composition disclosed by Koppel. Because the PTO has no means to conduct analytical experiments, the burden of proof is shifted to the Applicant to prove that the properties are not inherent. ""[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." MPEP § 2112, I.

Claims 1-7, 9-12, 16-20, 28-30 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel (WO 01121184, cited on PTO Form 1449) in view of Smith (Lancet, 1992).

Applicant Claims

The instant application claims a method of treating a subject suffering from or susceptible to ALS (elected species), the method comprising administering to the subject a therapeutic amount of a beta-lactam compound which is sufficient to treat the disease or disorder.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Koppel is directed to neurotherapeutic compositions and method. Claimed is a method of treating a human patient afflicted with a condition characterized at least in part by abnormal extracellular glutamate concentration in the brain or other nervous tissue. Claimed compounds include beta-lactams such as cephalosporins (claims 33-34 and 36). The condition claimed includes ALS (claim 39). Beta-lactam antibiotics taught include ceftriaxone and ceftriaxone sodium (page 38, lines 19-20). Parenteral dosages of the beta-lactams can range from about 1 to about 80 mg per dose (page 42, lines 11-12). Parenteral routes of administration include intramuscular and intravenous (page 45, lines 16-20). It is taught that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state (page 46, lines 12-23). The plasma concentration is around 50 pM (page 79 line 2).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Koppel suggest that ceftriaxone and ceftriaxone sodium can be utilized to treat ALS, Koppel does not exemplify this method of treatment. However, this deficiency is cured by Smith.

Smith teaches reports that ceftriaxone can be utilized to improve ALS (right column).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel and Smith and utilize ceftriaxone to treat ALS. One of ordinary skill in the art would have been motivated to utilize ceftriaxone to treat ALS as Koppel suggest this use and one of ordinary skill in the art would have been motivated to choose ceftriaxone out of all the beta-lactam antibiotics taught by Koppel as Smith recognizes that it can improve ALS.

Regarding the claimed amount of beta-lactam compound, Koppel teach overlapping amounts. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exists. **See MPEP 2144.05 [R-5].**

Regarding the claimed length of administration, Koppel teaches that the level of efficacy and optimal dosage and dosage form for any given protease inhibitor for use within the scope of the invention is patient-dependent and adjustable within reasonable ranges in the judgment of the attending physician. The formulation is typically administered over a period of time sufficient to treat the disease state. Therefore, the length of administration is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ and reasonably would expect success. It would have been customary for an artisan of ordinary skill to

determine the optimal amount of each ingredient to add in order to best achieve the desired results. It would have been obvious to one of ordinary skill in the art at the time of the invention to engage in routine experimentation to determine optimal or workable ranges that produce expected results. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F. 2d 454, 105 USPQ 233 (CCPA 1955).

It would have been obvious to one of ordinary skill in the art to utilize a kit for the administration of the beta-lactam. One of ordinary skill in the art would have been motivated to utilize a kit in order to package and ship the formulation as well as to provide instructions for a consumer/provider on how to utilize the product. "Where the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability." *In re Ngai*, 367 F.3d 1336, 70 USPQ2d 1862 (Fed. Cir. 2004). **See MPEP 2112.01 [R-3].** The applicant has not indicated that the instructions indicate some unobvious functional relationship between the product and the instructions.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Koppel (WO 0112184) in view of Smith and in further view of Khanna et al. (US Patent No. 5869649).

Applicant Claims

The instant application claims the beta-lactam is ceftriaxone disodium salt, sesquarterhydrate.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Koppel and Smith are set forth above. Specifically, Koppel teaches that beta-lactam compounds such as ceftriaxone sodium can be utilized to treat ALS. Smith confirms that administration of ceftriaxone has been shown to improve ALS patients.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

Koppel does not teach the ceftriaxone sodium is ceftriaxone disodium slat sesquarterhydrate. However, this deficiency is cured by Khanna et al.

Khanna et al. is directed to the preparation of cephalosporin antibiotics namely ceftriaxone sodium (abstract). Formation of ceftriaxone sodium results in the disodium salt hemiheptahydrate (example 3).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Koppel, Smith and Khanna et al. and utilize ceftriaxone disodium hemiheptahydrate (sesquarterhydrate) as Koppel teaches that ceftriaxone sodium can be utilized and Khanna et al. teaches that the formation of ceftriaxone sodium results in the formation of ceftriaxone disodium salt hemiheptahydrate.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Abigail Fisher
Examiner
Art Unit 1616

AF

/Abigail Fisher/

Examiner, Art Unit 1616